Interactions between sympathetic nervous system and endogenous endothelin in patients with essential hypertension

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Abstract: Experimental evidence indicates that endothelin 1 stimulates the sympathetic nervous system by activation of the subtype A receptor. The aim of the present study was to assess whether this mechanism is active in humans and to investigate its potential role in the pathogenesis of essential hypertension. In 15 hypertensive patients and 12 normotensive subjects, blood pressure, heart rate, and muscle sympathetic nerve activity were evaluated during intravenous 20-minute infusion of BQ123 (0.1 mg/kg per hour), an endothelin A receptor antagonist, and sodium nitroprusside (SNP; 0.4 g/kg per minute). In hypertensive patients, blood pressure was reduced similarly by BQ123 and SNP. In contrast, the increase in muscle sympathetic nerve activity induced by BQ123 (from 52.0±4.9 to 56.8±5.5 bursts per 100 heartbeats; $P<0.05$ versus baseline) was significantly lower ($P<0.05$) than that induced by SNP (from 50.6±4.9 to 61.1±5.1 bursts per 100 heartbeats; $P<0.05$ versus baseline). In normotensive subjects, SNP reduced blood pressure and increased muscle sympathetic activity, whereas BQ123 was ineffective. Thus, in a subgroup (n=9) of normotensive subjects, we administered BQ123 at a higher dose (0.2 mg/kg per hour), representing an equidepressor dose of SNP, inducing a blunted increase in sympathetic activity (from 44.1±2.4 to 50.1±6.4 bursts per 100 heartbeats; $P<0.05$ versus baseline). Finally, administration of a different vasodilator (papaverine, 0.5 mg/kg per hour) exerted results superimposable to SNP. Endogenous endothelin 1 appears to have a sympathoexcitatory effect both in normotensive and hypertensive subjects through endothelin A receptors, contributing to basal sympathetic vasomotor tone. Moreover, essential hypertension shows an increased susceptibility to the sympathoexcitatory effect of endogenous endothelin 1.

DOI: https://doi.org/10.1161/HYPERTENSIONAHA.110.163584

INTERACTIONS BETWEEN SYMPATHETIC NERVOUS SYSTEM AND ENDOGENOUS ENDOTHELIN IN PATIENTS WITH ESSENTIAL HYPERTENSION

Short title: endothelin and sympathetic nervous system

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Total word count: 4895

Journal Subject Codes [85] Autonomic, reflex, and neurohumoral control of circulation

[193] Hypertension, Clinical studies

Abstract

Rationale: Experimental evidence indicates that endothelin-1 stimulates sympathetic nervous system by activation of the subtype-A receptor. Aim of the present study was to assess the role of endogenous endothelin-1 in modulating sympathetic activity in essential hypertensive patients and in normotensive subjects.

Methods and Results: In 15 hypertensive and 12 normotensive subjects blood pressure, heart rate and muscle sympathetic nervous activity were evaluated during intravenous 20' infusion of BQ123 (0.1 mg/Kg/h), an ET_A-receptor antagonist, and sodium-nitroprusside (0.4 µg/Kg/min). In hypertensive patients, blood pressure was similarly reduced by BQ123 and sodium-nitroprusside. In contrast, the increase in muscle sympathetic nervous system activity induced by BQ123 (from 52.0±4.9 to 56.8±5.5 bursts/100hb, $p<0.05$ vs baseline) was significantly lower ($p<0.05$) than sodium nitroprusside (from 50.6±4.9 to 61.1±5.1 bursts/100hb, $p<0.05$ vs baseline). In normotensive subjects, BQ123 did not modify blood pressure or sympathetic activity, but caused a significant increase in heart rate. In a subgroup (n=9) of normotensive subjects we administered BQ123 at a dose (0.2 mg/Kg/h) equidepressor to sodium nitroprusside, inducing a blunted increase in MSNA (from 44.1±2.4 to 50.1±6.4 bursts/100hb, $p<0.05$ vs baseline). The use of a different vasodilator (papaverine, 0.5 mg/Kg/h) exerted results superimposable to sodium nitroprusside.

Conclusions: Endogenous endothelin-1 appears to have a sympatoexcitatory effect both in normotensive and hypertensive subjects through ET_A receptors, contributing to the basal sympathetic vasomotor tone. Moreover essential hypertension shows an increased susceptibility to sympathoexcitatory effects of endogenous ET-1.

Key Words: hypertension • sympathetic nervous system • endothelin •

Introduction

Essential hypertension is characterized by an increased sympathetic nervous system (SNS) activity, as clearly demonstrated by means of sensitive techniques, such as the norepinephrine spillover method[1] and the microneurographic quantification of nerve traffic[2]. SNS activation is already present in normotensive offspring of hypertensive patients[3], is peculiar of the essential hypertensive state[2], parallels the degree of blood pressure (BP) increase[2] and may exert deleterious metabolic and cardiovascular effects, accelerating the progression of the target organ damage associated with hypertension[4].

Endothelin-1 (ET-1) is a vasoconstrictor and mitogenic peptide produced by endothelial cells and its important role in regulation of vascular tone and structure is well established [5]. Essential hypertension is characterized by increased ET-1 vasoconstrictor tone[6-7], which seems to be a consequence of reduced availability of nitric oxide (NO)[7]. ET-receptor antagonists, particularly those acting on ET_A receptors, are a promising therapeutic option in patients with resistant[8] and renoparechimal[9] hypertension. The endothelin system role in cardiovascular homeostasis is not limited to its direct vascular effects, but involves also the neural regulation of vasomotor tone[10]. Experimental evidence suggests that ET-1 can stimulate central and peripheral SNS activity through ET_A receptors[11-12]. While intracerebral administration of ET-1 can increase blood pressure and SNS activity mainly through ET_A receptors in hypertensive as well in normotensive animals[11-12], the administration of an ET_A receptor antagonist determines the opposite effect only in hypertensive animals, suggesting a specific sympathoexcitatory role for the endothelin system in this condition[11]. With regard to the peripheral autonomic

nervous system, ET-1 can act in carotid bodies and in cervical superior and nodose ganglia, influencing baroreflex and chemoreflex regulation; is released by post-ganglionic sympathetic neurons, possibly modulating catecholamines release and vascular tone; and stimulates catecholamines release from adrenal glands[13]. Despite the growing body of evidence coming from experimental studies, few data are available about the systemic interaction between endogenous ET-1 and SNS in humans either in physiological or pathological conditions. Interestingly, local infusion of ET-1 is able to potentiate SNS-mediated vasoconstriction induced by deep breath[14]. Thus, we speculated that ET-1 could modulate sympathetic activity also in humans through ET_A receptors, and that this interaction could be peculiar for the hypertensive status. For this purpose, we evaluated the effect of systemic ET_A receptor blockade on SNS activity in healthy subjects and in patients with essential hypertension.

Methods

Population

The present study included 15 essential hypertensive patients (HT), enrolled by the Hypertension outpatient Clinic of the University Hospital of Pisa, and 12 healthy subjects (NT), recruited among the hospital staff.

The patients had never received any antihypertensive treatment and were characterized by mild essential hypertension (systolic BP between 140 and 159 and/or diastolic BP between 90 and 99 mmHg on repeated clinic measurements), no history or physical or laboratory evidence of overt cardiovascular disease, target organ damage or major non cardiovascular diseases. Current cigarette smoking and daily assumption of three or more alcohol drinks were considered as exclusion criteria. Secondary hypertension was excluded by standard testing. The two groups were comparable for age, body mass index, glycemic and lipid profile and renal function (Table 1).

The protocol of the study was approved by the local ethical committee and was in accordance with institutional guidelines. The patients gave their written informed consent to participate in the study after explanation of its nature and purpose.

Measurements

In each subject a detailed medical history and physical examination, BP (3 measurements in the sitting position by means of the automatic device Omron 705IT) and heart rate, anthropometric parameters and routine blood sample assays were measured before the inclusion in the study.

During the experimental session, the following measurements were obtained:

1) beat-to-beat BP through a finger photoplethysmographic device (Finapres 2300, Ohmeda; Englewood, Colorado);

2) beat-to beat heart rate, through a transthoracic ECG lead (Biotach, Gould Electronics; Valley View, Ohio);

3) plasma norepinephrine (NE) and epinephrine (E), both assayed by high-pressure liquid chromatography[15], and ET-1, by enzyme immunoassay (Biomedica, Wien), on venous blood samples taken from an antecubital vein;

4) multiunit recording of efferent postganglionic muscle sympathetic nerve activity (MSNA). Briefly, a tungsten microelectrode (diameter 200 μm), with a uninsulated 1-5 μm diameter tip (Medical Instruments, University of Iowa; Iowa City) was transcutaneously inserted into the right or left peroneal nerve just posterior to the fibular head. A reference electrode was inserted subcutaneously 1-3 cm from the recording site. The signal was integrated with a 0.1 second – time constant, amplified with a gain of 50000-80000, band-pass filtered (700-2000 Hz) and acquired with a sampling rate of 1000 Hz through a digital acquisition system (ACQ-16, Gould Electronics; Valley View, Ohio). MSNA was identified according to the criteria outlined in previous studies[3, 16-17], and in detail: electrical stimulation (0.1 to 0.3 V, 0.1 ms, 1 Hz) through the electrode in the peroneal nerve elicited involuntary muscle contractions in the peroneal nerve but no paresthesia; tapping or stretching the innervated muscle region elicited afferent mechanoreceptor discharges, whereas stroking the skin did not; spontaneous pulse-sincronous bursts, that increase in frequency during voluntary apnoea but not after a loud noise, were displayed by the neurogram. The recording was considered acceptable if the signal-to-noise ratio exceeded the value of 3. The neurograms so obtained were recorded together with BP and heart rate by means of a dedicated computer

software (Ponemah, LDS; Valley View, Ohio). MSNA was quantified as bursts per minute (bursts/min) and bursts per 100 heart beats (bursts/100hb). MSNA recordings were analyzed by visual inspection by a single investigator, blinded about the protocol of the study and the infused drug. The coefficient of variation of MSNA at different time intervals in the same individual in our laboratory is 4.4%. During the recording, respiration rate was monitored through a strain-gauge pneumograph (Pneumotrace, Gould Electronics; Valley View, Ohio), positioned at the midchest level, in order to exclude from the data analysis any time interval in which respiratory rhythm alterations were present.

Experimental protocol

All experimental sessions were performed in the morning, and the subjects were asked to avoid smoking, caffeine- and alcohol-containing beverages, and eating for the 12 hours before the study. During the experimental session, the subjects were put in the supine position in a quiet and comfortable room and then fitted with an intravenous cannula, the microelectrodes for MSNA recording, and the other measuring devices. After a 30-minute interval, BP, heart rate, respiration rate, and MSNA were continuously monitored and recorded in baseline conditions and during infusion of a selective antagonist for ET_A receptors, BQ-123 (Clinalfa, Bachem; Weil am Rhein, Germany), at the dose of 0.1 mg/Kg/h, and of a direct vasodilating agent, sodium nitroprusside (SNP; Malesci; Florence, Italy), at the dose of 0.4 µg/Kg/min. Each drug was infused for 20 minutes and was preceded by a 10-minute baseline acquisition. Because of the prolonged pharmacodynamic effect of BQ123[18], it was not possible to randomize the two drug infusions in each experimental session. Thus

SNP, having a very short half-life, was always infused as the first drug, allowing a 30-minute wash out period before the beginning of BQ123 infusion. In 4 NT and 6 HT, two experimental sessions were performed (separated by at least two weeks each other), administering in one session SNP and BQ123 and in the other session normal saline infusion (NaCl 0.9%), and the vasodilator drug papaverine (0.5 mg/kg/h i.v.). The order of the two sessions was randomized. The doses of SNP and papaverine were chosen according to preliminary studies in order to obtain the same BP reduction as BQ123 in the hypertensive population. Given the known smaller vasodilatory power of BQ123 in healthy subjects[9], 9 out of 12 NT underwent an adjunctive experimental session, administering BQ123 at the dose of 0.2 mg/kg/h. Blood samples for NE, E and ET-1 were collected at baseline and at the end of each drug infusion.

Data Analysis

Statistical analysis was performed by NCSS 2007 (Kaysville, Utah). Results are shown as mean ± standard deviation. Differences in baseline characteristics between groups were analyzed by unpaired t-test or χ^2, as appropriate. BP, heart rate, and MSNA obtained in each subject were averaged for intervals of 10 minutes during the baseline period and of 5 minutes during drug infusion. Within each group, repeated measurements were analyzed by general linear model ANOVA, considering as factors time intervals and type of drug, and Fisher‘s LSD multiple comparison post-hoc test. A p level less than 0.05 was used to define statistical significance. The sample size was calculated in order to reject the null hypothesis with a power of 0.8 and a type I error probability of 0.05. The minimum number of patients required to

demonstrate a difference in MSNA of 6 bursts/100hb above baseline, with a standard deviation of 5 bursts/100hb, is 8 for each study group.

Results

Baseline Values

Table 1 shows the clinical characteristics of the study population. BP and MSNA values were, as expected, higher in HT as compared to NT. The other parameters were similar in the two groups.

Hemodynamic parameters

In HT, BP values were significantly reduced both by BQ123 (systolic BP from 149.4±10.0 to 145.5±10.9 mmHg, $p<0.01$; diastolic BP from 91.1±7.5 to 87.8±7.6 mmHg, $p<0.05$) and SNP (systolic BP from 150.9±11.7 to 146.1±13.0 mmHg, $p<0.01$; diastolic BP from 90.6±8.6 to 87.3±9.6 mmHg, $p<0.05$) to a similar extent (Figure 1a). On the contrary, in the control group SNP and BQ123 infusion exerted different results, since the former significantly reduced systolic (from 129.2±11.1 to 125.5±11.8 mmHg; $p<0.05$) and diastolic BP (from 77.0±9.3 to 73.7±8.8 mmHg; $p<0.05$), whereas the latter did not modify BP values (systolic BP from 130.3±11.6 to 129.2±12.6 mmHg, p=ns; diastolic BP from 76.9±9.8 to 76.6±9.7 mmHg, p=ns) (Figure 1b).

In HT, heart rate was significantly increased both by BQ123 (from 69.8±10.8 to 78.2±13.1 bpm, $p<0.01$) and SNP (from 71.1±8.8 to 80.0±12.4 bpm, $p<0.01$) (figure 1e). In NT, heart rate was increased by SNP infusion (from 68.7±7.0 to 81.0±6.8 bpm; $p<0.001$ vs baseline), to a greater extent as compared to HT ($p<0.05$ vs HT), despite a similar BP-lowering effect; BQ123 infusion caused a small but significant increase in heart rate (from 69.0±5.8 to 74.9±9.0 bpm, $p<0.05$) in absence of any BP change (figure 1f).

Hemodynamic responses to SNP and papaverine infusion were similar both within the hypertensive (systolic BP-3.2±1.9% vs -3.0±2.1%; diastolic BP -3.8±1.2% vs -3.2±2.1%; heart rate +11.3±5.5% vs +11.3±5.5%; p=ns for all) and the control group (systolic BP -3.1±2.4% vs -2.9±2.0%; diastolic BP -4.1±1.7% vs -4.6±1.8%; heart rate +18.3±6.3% vs +16.6±4.0%; p=ns for all). Placebo infusion did not exert any significant change in systolic BP (HT from 148.0±9.0 to 149.7±10.7 mmHg; NT 126.4±12.7 to 126.0±10.3 mmHg; p=ns for all), diastolic BP (HT from 88.7±7.1 to 87.0±8.9 mmHg; NT 78.0±10.4 to 77.0±10.4 mmHg; p=ns for all), or heart rate (HT from 69.4±8.2 to 70.6±9.4 bpm; NT 65.5±5.6 to 64.2±6.8 bpm; p=ns vs for all).

Muscle sympathetic nerve activity

In HT, even in presence of similar hemodynamic modifications, the effect of the two vasoactive drugs on MSNA was different. MSNA was significantly increased by SNP infusion (from 50.6±4.9 to 61.1±5.1 bursts/100hb, $p<0.01$). Of note, the increase in MSNA induced by BQ123 (from 52.0±4.9 to 56.8±5.5 bursts/100hb, $p<0.05$) was significantly lower ($p<0.05$) as compared to the one induced by SNP (Figure 2a).
In NT, the effect of SNP infusion on MSNA (from 43.1±4.2 to 52.3±9.1 bursts/100hb, $p <0.001$) was similar to that observed in HT, while BQ123 infusion did not significantly modify MSNA (from 43.7±3.9 to 44.4±3.5 bursts/100hb, p=ns), as well as blood pressure (Figure 2b).
SNP and papaverine infusion induced a similar MSNA increase within the hypertensive (+21.5±10.5% vs +23.7±9.0%; p=ns) and the control group (+22.4±13.4% vs +25.6±12.8%; p=ns). Finally, MSNA was not modified by placebo infusion either in HT (from 52.1±5.1 to 53.6±0.7 bursts/100hb, p=ns) or in NT (from 44.9±2.7 to 46.4±5.0 bursts/100hb, p=ns).

Neurohumoral parameters

At baseline, plasma concentrations of NE, E and ET-1 were similar in HT and in NT (Table 1). After infusion of BQ123 they were not significantly modified either in HT (NE 2.2±0.6 nmol/l, E 146±39 pmol/l, ET-1 1.9±0.3 fmol/l) or in NT (NE 1.9±0.8 nmol/l, E 108±46 pmol/l, ET-1 1.6±0.6 fmol/l). Also infusion of SNP, placebo and papaverine did not modify plasma concentrations of the assayed parameters (data not shown).

Responses to high dose BQ123

In 9 NT the experimental session was repeated administering BQ123 at the dose of 0.2 mg/kg/h, in order to obtain a significant BP-lowering effect. Higher doses of BQ123 effectively reduced BP (systolic BP from 130.1±7.1 to 124.6±6.7 mmHg, $p<0.05$; diastolic BP from 77.0±7.9 to 73.2±7.7 mmHg, $p<0.05$), as represented in figure 1b. BP decrease was comparable to that induced by SNP (p=ns), while the increase in heart rate (from 67.7±6.0 to 73.5±7.6 bpm, $p<0.05$), was still significantly smaller as compared to SNP (figure 1d). High-dose BQ123 also induced an increase in MSNA (from 44.1±2.4 to 50.1±6.4 bursts/100hb, $p<0.05$), which was blunted as compared with SNP ($p<0.05$, figure 2b).

Discussion

The main finding of this study is that the reduction in BP induced by the acute intravenous administration of an ET_A -antagonist produces a blunted increase in SNS activity in patients with essential hypertension and in healthy subjects. This finding suggests that endogenous ET-1, by the stimulation of ET_A receptors, contributes to the basal sympathetic tone that controls vascular resistances in humans. Moreover in HT, as compared to NT, lower doses of BQ123 were sufficient to reveal the vasodilating and sympathoinhibitory effect of ET_A blockade. Thus, our results confirm that endogenous ET-1 exerts a stronger vasoconstrictor effect in HT than in NT[7] and demonstrate for the first time that essential hypertension is characterized by a greater susceptibility to the sympathoexcitatory effect of endogenous ET-1. Because experimental studies pointed on the role of ET_A receptors as the mediators of the effect of ET-1 on SNS[11-12], we decided to use a selective antagonist for this ET-receptor subtype. To distinguish a potential direct effect of BQ123 on sympathetic nerve activity from the aspecific, baroreflex-mediated, effect due to BP lowering per se, BQ123 was compared with SNP, a direct vasodilating drug. In patients with essential hypertension, both BQ123 and SNP induced a similar BP reduction, with a parallel increase in heart rate. Nevertheless, despite similar hemodynamic modifications, the increase in MSNA measured by microneurography was significantly smaller during BQ123 infusion than during SNP infusion. In other words, the expected baroreflex-mediated increase in MSNA, induced by any BP lowering drug, appeared to be blunted by a direct effect of the ET_A blockade. Thus, ET-1 seems to have a stimulating effect on sympathetic nerve activity through the activation of ET_A receptor subtype.

When the same experimental protocol was applied to NT, SNP determined similar changes in BP and MSNA as compared to HT. In contrast, BP and MSNA were not modified by BQ123 administration. The absence of any hemodynamic effect in response to BQ123 infusion was expected according to the previous literature[9, 18-19], indicating a less potent vasoconstrictor effect of endogenous ET-1 in NT than in patients with essential hypertension[6-7]. For that reason in NT we re-administered BQ123 at a higher dose, capable to induce the same BP reduction obtained in HT. In that conditions we observed a significant increase in MSNA, which however was blunted in comparison to that induced by SNP infusion. The results were further confirmed by the fact that another vasodilator, such as papaverine, exerted a similar BP and MSNA response as compared to SNP, thus highlighting the peculiarity of ET_A-blockade effect and excluding a direct effect of exogenous NO released by SNP on sympathetic activity.

Our results demonstrate that endogenous ET-1 contributes to the modulation of SNS activity both in physiological conditions and in essential hypertension. Furthermore, HT patients, which are characterized by an increased vasoconstriction to endogenous ET-1, as previously demonstrated by our group[7], present also a greater susceptibility to the sympatoexcitation due to endogenous ET-1. Taken together, these findings suggest that the increased biological activity of endogenous ET-1 of HT takes place in parallel in different systems, such as in the peripheral vasculature and in the SNS. Although the small entity of the BP reduction obtained with BQ123 infusion could suggest a limited relevance of the contribution of ET-1 in BP regulation, it is conceivable that the pressor effect of ET_A antagonism might be buffered by baroreflex mechanisms in this population of relatively young subjects.

Experimental data support the hypothesis of a role of endogenous ET-1 in modulation of central sympathetic drive[11-12, 20-21], which is enhanced in some experimental models of hypertension[11, 22]. BQ123 is able to cross the blood-brain barrier, possibly through an active transport system[23], and thus to block ET_A-mediated effects of endogenous ET-1 in several sites within the central nervous system[13]. Moreover BQ123 could act on brain areas characterized by an incomplete blood-brain barrier, like area postrema[21], which could be a key site of action of ET-1 within central nervous system[24]. Another possible site of interaction could be at the level of sympathetic postganglionic neurons within the sympathetic ganglia[13].

As expected, during SNP infusion the increase in heart rate was blunted in HT in comparison to NT, confirming the presence of a reduced heart rate-baroreflex gain, which is a well established feature of essential hypertension[2]. During administration of BQ123 in healthy subjects, an increase in heart rate was observed even in the absence of any BP modification, leading to different interpretations. Previous studies[9, 18] demonstrated that subpressor doses of BQ123 reduce systemic vascular resistances, possibly via activation of cardiopulmonary reflexes. Another hypothesis is a direct chronotropic effect, recently highlighted in healthy conscious rats after the administration of the non selective ET_A-ET_B receptor antagonist bosentan[25].

Interestingly, using higher doses of BQ123 in order to induce a significant hemodynamic effect, BP reduction was accompanied by a blunted heart rate response as compared to SNP. Pedersen and colleagues found a superimposable heart rate increase as compared to our results, but they attributed it only to the reflex response to vasodilation, because they did not compare BQ123 effect with another

vasodilator[19]. Our results are in agreement with experimental observations in which ET-1 increased heart rate-baroreflex gain [26-27], while bosentan administration caused opposite effects [25]. These data suggest a specific physiological role for ET_A receptors in regulation of heart rate, which is not evident in essential hypertension and needs to be further investigated.

Plasma NE concentrations were not significantly modified during the infusion of BQ123 in HT as well as in NT. However this result is not necessarily in contradiction with MSNA results, because plasma NE can be considered only a very rough index of the spillover of the neurotransmitter from vascular sympathetic terminations[28]. Moreover the endothelin system modulates NE release at presynaptic sympathetic nerve endings, but also from the adrenal glands[13], further limiting the use of plasma NE for the estimation of sympathetic activity in the present study.
Plasma ET-1 concentrations, according to literature, were similar in HT and NT[29] and they were not modified by BQ123[18]. This observation could be explained by the fact that plasma levels of the peptide does not reflect its biological activity, since ET-1 is released mainly abluminally and removed by plasma mainly by binding with ET_B receptors[5].
Among the limitations of the study, it has to be taken into account the short-lasting monitoring of the hemodynamic parameters and of MSNA. The study was designed according to previous studies[18], showing that the time interval is sufficient to obtain detectable hemodynamic changes. However, since this is the first study exploring sympathetic nerve activity during ET_A inhibition, we cannot exclude further MSNA variations in the following period. Our findings are also limited by the absence of any measurement of central venous pressure, a key determinant of sympathetic activity.

While it is well established that the SNP-induced sympathoexcitation is determined both by BP and central venous pressure reduction, little information is available about the effects of ET_A blockade. Dorsal hand venoconstriction to ET-1 is greater in HT than in NT[14]. Thus, it is conceivable that ET-1-inhibition should result in a greater increase in venous capacitance and reduction in central venous pressure in HT than in NT, in parallel to what happens in the arterial district. On the other hand, since sympathetically mediated venoconstriction is potentiated by ET-1 in HT in comparison to NT[14], we can speculate that ET-antagonism could blunt sympathetic responses to central venous pressure changes. Thus, the ET/SNS interaction in the venous district could contribute to the blunted MSNA response to BQ123 in HT in the present study.

Perspectives

Our results demonstrate that endogenous ET-1 has a sympatoexcitatory effect both in physiological conditions and in essential hypertension, possibly contributing to the basal sympathetic outflow regulating vasomotor tone. Furthermore, essential hypertension appears to be characterized by an increased susceptibility to the sympathoexcitatory effect of endogenous ET-1. Thus, the discovery of an enhanced biological activity of ET-1 on autonomic cardiovascular regulation, beyond the known effects on vascular tone, further reinforces the fundamental role of the endothelin system in the pathophysiology of essential hypertension and of the related organ damage. Thus, treatment options aimed at contrasting the endothelin system could favourably influence adrenergic overactivity characterizing essential hypertension.

Acknowledgements: None.

Sources of founding: None.

Disclosures: None

Figures legend

Figure 1: The figure shows the behavior of systolic blood pressure (figure 1a and 1 b) and heart rate (figure 1c and 1d) during the experimental sessions in hypertensive patients, on the left, and in normotensive subjects, on the right. Empty circles represent data during SNP infusion, black circles during BQ123 infusion at 0.1 mg/kg/h and grey circles during BQ123 infusion at 0.2 mg/kg/h. Data are shown as mean±SEM. BP: blood pressure; * $p<0.05$ vs baseline; † $p<0.05$ vs SNP.

Figure 2: The figure shows the behavior of muscle sympathetic nerve activity during the experimental sessions in hypertensive patients (2a), and in normotensive subjects (2b). Empty circles represent data during SNP infusion, black circles during BQ123 infusion at 0.1 mg/kg/h and grey circles during BQ123 infusion at 0.2 mg/kg/h. Data are shown as mean±SEM.
MSNA: muscle sympathetic nerve activity; b/100hb bursts: per 100 heart beats; * $p<0.05$ vs baseline; † $p<0.05$ vs SNP.

Table 1. **Clinical characteristics of the Study Population**

	Hypertensive Patients (n=15)	**Normotensive Subjects (n=12)**
Age (years)	45.8±6.8	43.5±5.6
Gender (M/F)	11/4	9/3
Systolic BP (mmHg)	150.9±11.7*	130.1±7.1
Diastolic BP (mmHg)	90.6±8.6*	82.0±7.9
Heart rate (bpm)	71.1±8.8	68.7±7.0
MSNA (bursts/min)	34.1±8.9*	29.4±2.4
MSNA (bursts/100hb)	50.6±9.9*	43.1±4.2
BMI (Kg/m^2)	23.8±4.1	22.2±3.5
Total Cholesterol (mmol/l)	5.1±0.9	5.0±0.6
HDL-cholesterol (mmol/l)	1.2±0.4	1.3±0.5
LDL-cholesterol (mmol/l)	3.0±0.6	2.8±0.7
Blood glucose (mmol/l)	5.2±0.2	4.9±0.4
Plasma creatinine (µmol/l)	80.0±13.1	78.3±9.1
NE (nmol/l)	1.9±0.6	1.6±0.8
E (pmol/l)	147±27	121±42
ET-1 (fmol/l)	1.7±0.5	1.7±0.8

M: male; F: female; BP: blood pressure; MSNA: muscle sympathetic nervous activity; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NE: norepinephrine; E: epinephrine; ET-1: endothelin-1; *: $p<0.05$ vs normotensive subjects.

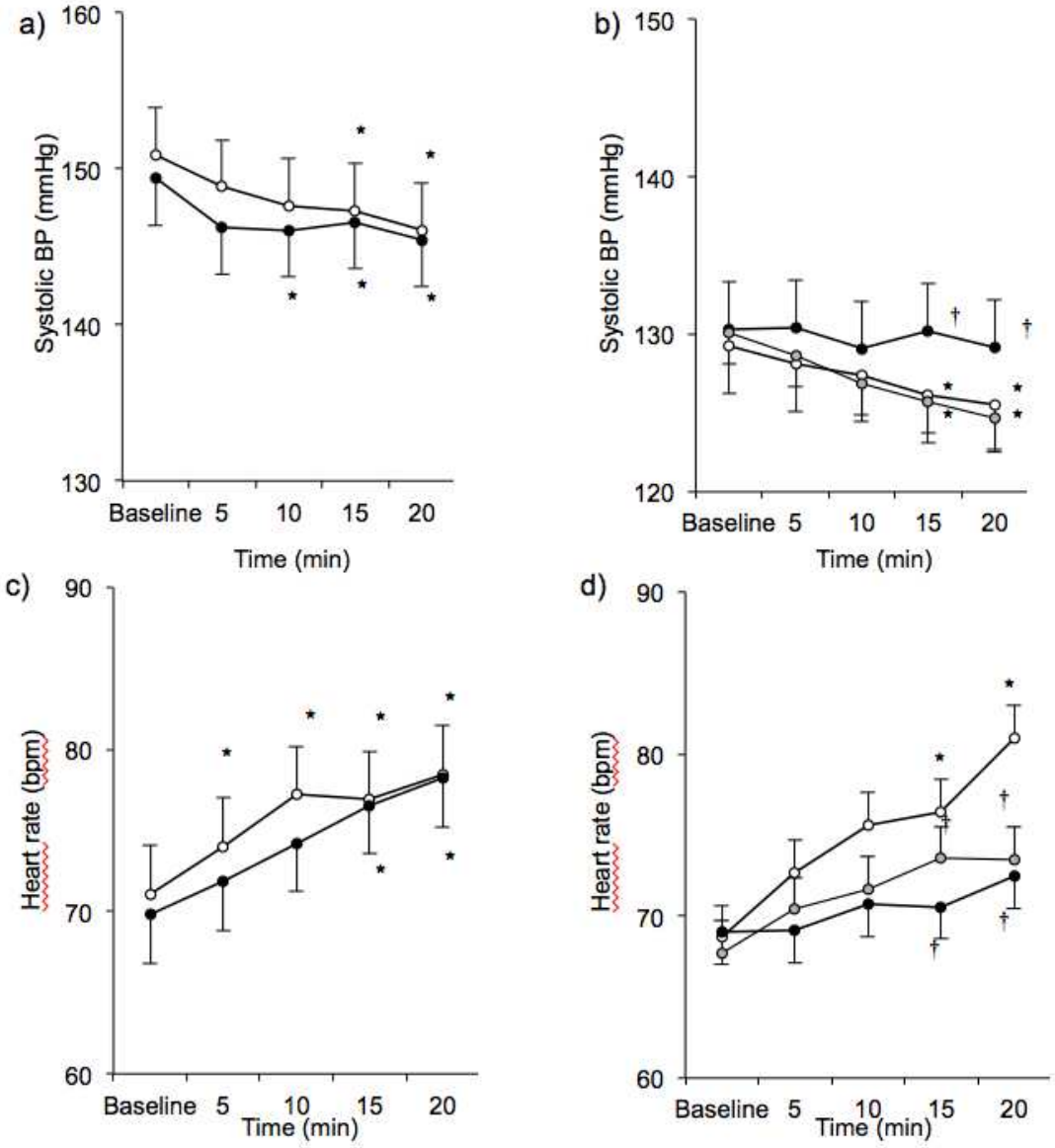
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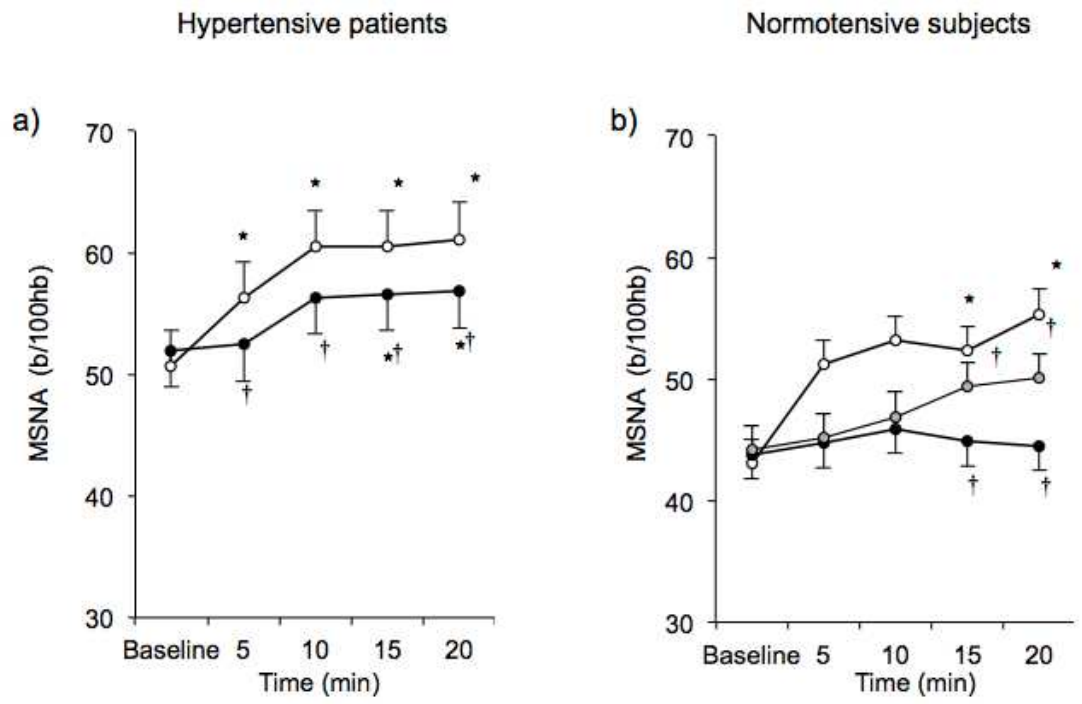
Figure 1


Hypertensive patients
Normotensive subjects
a)
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15
20
Time (min)

Figure 2

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